CJD and human prion disease

Introduction

Prion (pronounced “pree-on”, or “pry-on”) diseases are rare, fatal brain disorders, affecting humans and certain animals. Although they can develop from various causes, once developed these diseases can be transmitted (like infections) between individuals of the same or different species. Prion diseases began attracting public attention in the mid 1980s, due to BSE (Bovine Spongiform Encephalopathy), a prion disease of cattle. Although the origin of the disease remains unknown, the BSE epidemic was spread by contamination of animal feed with tissues from BSE-infected cattle.

In humans, the best-known prion disease is CJD (Creutzfeldt-Jakob disease), which strikes about one to two in a million persons each year, resulting in around 35 new cases a year in Canada. CJD can be subdivided into three different subtypes – genetic, acquired and sporadic – based on how the disease is caused. Sporadic CJD, which occurs unpredictably, accounts for over 90 per cent of Canadian CJD cases. At least 7 per cent of human prion disease cases in Canada are caused by genetic abnormalities (mutations), and these are known as genetic prion disease. Acquired prion disease occurs when the disease is transmitted by infection between members of the same or different species. There have been a few Canadian CJD cases that resulted from accidental transmission of infections during medical procedures; this is known as iatrogenic CJD. Variant CJD (vCJD), which affects primarily younger people, is almost certainly caused by exposure to BSE-contaminated food. Variant CJD has occurred in Canada, but it is extremely rare.

The brains of people or animals with prion disease undergo damage, called “spongiform change” or “spongiosis” because when the tissue is examined under a microscope it looks like a sponge, with many tiny holes. In addition, the brain tissue contains abnormal deposits of a specific protein called PrP. In vCJD, a distinctive pattern of spongiform change occurs, where the holes are particularly numerous around dense microscopic protein deposits called plaques. These structures, which are sometimes called “daisy plaques” or “florid plaques” because the deposits with their surrounding holes suggest the shape of a flower, are used by the pathologist to help distinguish vCJD from other forms of CJD.

Many brain cells die in CJD, and many different brain areas with different functions can be affected. This explains why symptoms ranging from dementia (loss of memory and thinking abilities) to movement disorders such as ataxia (difficulty walking and balancing) or myoclonus (jerking limb movements) can be seen in the patient. The wide variety of symptoms in CJD can make the diagnosis very difficult for a doctor, especially in early stages of disease. Some specialized procedures and laboratory tests can be performed to help with diagnosis, but a final decision on whether a person has CJD or not can only be made by examination of the brain after death.

The different kinds of human prion diseases, and their main characteristics, are summarized in the table below.

Human prion diseases: Types, causes and distinguishing features

TYPE	CAUSE	DISTINGUISHING FEATURES
Sporadic CJD	Unknown	• Affects mainly people over 50. • Ataxia, dementia, myoclonus. • Short period of illness. • Spongiform change, rarely plaques.
Genetic prion disease	Inherited genetic abnormalities (mutations)	• Slightly younger onset than sporadic CJD. • Symptom pattern depends on type of mutation, but sometimes like sporadic CJD. • Period of illness may be longer.
Acquired prion disease	Infectious transmission	Various (see below)
Iatrogenic CJD	• Contamination through brain surgery, corneal transplant, dura mater graft, human growth hormone. • Transfusion-associated vCJD transmission.	• Younger onset than sporadic CJD. • Ataxia rather than dementia. • Growth hormone-related cases show plaques.
Variant CJD	Exposure to BSE	• Young onset. • Psychiatric features and longer period of illness. • Distinctive florid plaques.

Prions: Infectious proteins in CJD

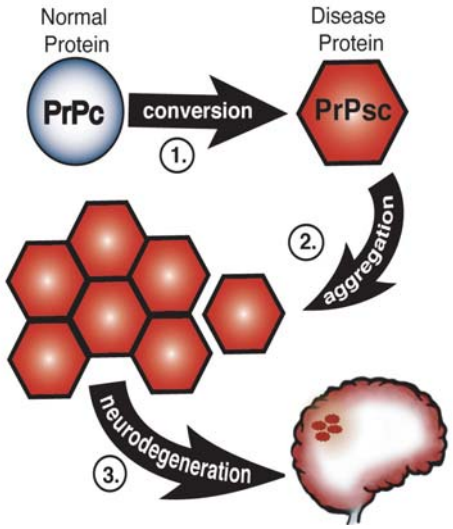
Proteins are one kind of basic, sub-microscopic biochemical building block of which living organisms are composed. They are long, linear molecules made up of hundreds of smaller chemical units called amino acids, joined together like links of a chain. DNA, which is also a linear biomolecule, carries the coded information to make each of the tens of thousands of different types of proteins made by the human body. Each protein is encoded by its own gene, located in a specific segment of the DNA. Protein molecules are fairly flexible and typically fold back on themselves to adopt a number of subtly different three-dimensional shapes. Once formed and folded within a cell, a protein molecule carries out one or a few of many different possible activities essential for life, such as transport of materials, transmission of information, or release of energy.

The prion protein, or PrP, is encoded by a gene called *PRNP*. PrP can exist in two main folded shapes, normal and abnormal. For convenience, these are called PrP^{C} and PrP^{Sc}. PrP^{C} is found in the human brain and in other parts of the body, where it performs an as-yet-unknown function. PrP^{C} is also found in all other mammals and even in birds.

Unlike PrP^{C}, PrP^{Sc} is resistant to normal cellular processes that would break it down and remove it from the body. As a result, it accumulates in the brain of a patient with a prion disease. As mentioned above, in some cases PrP^{Sc} forms deposits called amyloid plaques – protein clumps (aggregates) that are particularly resistant to breakdown and removal. Plaques consisting of misfolded proteins are also found in other diseases, such as Alzheimer's disease, and even in the normal aging brain, but in those cases proteins other than PrP are involved. PrP^{Sc} also forms tiny fibres called scrapie-associated fibrils (SAFs), which can be seen under a powerful microscope.

Abnormal forms of PrP are widely believed to be, or to contain, the infectious agents associated with prion diseases; hence the origin of the term "prion" – from *pr*oteinaceous *i*nfectious particle (Greek suffix "-*on*").

The central idea is that a single molecule of PrP^{Sc} can convert molecules of PrP^{C} into the abnormal form, by inducing them to adopt the abnormal shape. These newly converted molecules can convert more normal molecules, leading to a cascade effect that would eventually lead to brain damage. In forms of CJD acquired by infectious transmission (iatrogenic CJD and vCJD), PrP^{Sc} molecules are presumed to enter the body from an external source (such as another affected human or animal) and to start converting the PrP^{C} molecules of their new "host". It has been suggested that occasionally a molecule of PrP^{C} spontaneously converts into the abnormal form, which could lead to further conversion and eventual development of sporadic CJD. In genetic prion disease, affected individuals carry genetic mutations in their *PRNP* gene. Individuals with *PRNP* mutations may produce forms of the PrP^{C} molecule that are more likely to be converted into PrP^{Sc}.



Normal protein converts to disease causing protein, and replicates causing spongy holes in the brain.

Specific Features of CJD Subtypes

Sporadic CJD

"Sporadic" means "occurring occasionally or unpredictably". No obvious risk factors have been discovered for sporadic CJD.

Sporadic CJD is most common in the 45-75 age group. Outside this age group it is rare, and the peak age of onset is 60-65. The total rate of occurrence of new cases of sporadic CJD is around one to two per million population per year – that is, around 35 new cases in Canada every year.

Extensive research has revealed no obvious risk factors (contributing causes) for developing sporadic CJD. Men are as likely to get it as women, and there is no link with any particular occupation. Of course, great attention has been paid to the diets of people with all forms of CJD, to search for any link with foods such as beef. This research has not shown any evidence that diet represents any risks for sporadic CJD.

Although it is not directly caused by genetic mutations, sporadic CJD is influenced by genetics. Two normal versions (alleles) of the *PRNP* gene (called 129M and 129V respectively) occur widely in the human population. These variants do not cause prion disease, but rather influence a person's risk of disease and the form the disease takes if it does occur. Each person inherits two copies of the *PRNP* gene – one from their father and one from their mother. Therefore, an individual can carry two copies of 129M ("MM" genotype), two of 129V ("VV" genotype), or one of each ("MV" genotype). 70-80% of people with sporadic CJD carry the MM genotype, suggesting that when this rare disease occurs, whatever the cause, it is more likely to lead to disease in this genetic background.

What are the symptoms and disease course of sporadic CJD?
Sporadic CJD appears without warning, and the pattern of symptoms may vary from person to person.

- Early symptoms are like those of depression – mood swings, memory lapses, social withdrawal and lack of interest.

- After this brief period, rapid progression of the disease occurs. Symptoms can be a mix of rapidly progressive dementia (loss of memory and thinking abilities); ataxia (the patient becomes unsteady on his/her feet, lacking in coordination, and markedly clumsy); vision problems including blindness; rigidity of limbs and myoclonus (sudden jerky movements). Speech may become more difficult or slurred. Swallowing may become difficult and feeding by a tube may become necessary.

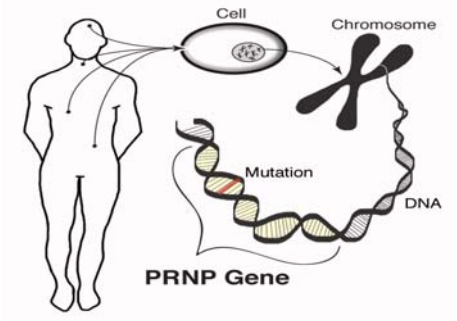
- Eventually the patient loses the ability to move or speak and they will require full-time nursing care. In this state, known clinically as akinetic mutism, the patient's eyes can still move and they may appear to be following what is going on around them, but in fact the patient is not aware of their surroundings at this stage.

- 65 per cent of sporadic CJD patients die within six months of the onset of symptoms. 15 per cent of patients have a disease duration of more than 1 year. Rarely, sporadic CJD lasts for several years.

Genetic Prion Disease

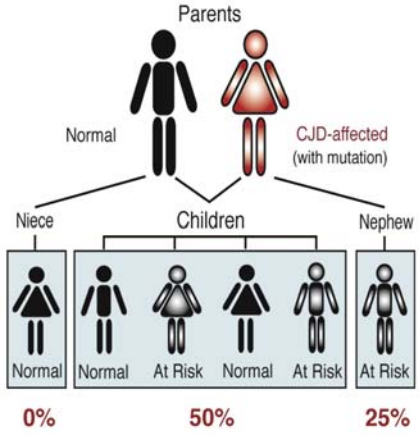
"Genetic" means that the disease is caused directly by genetic abnormalities in the gene, PRNP, that encodes the prion protein.

Genetic prion diseases account for at least 7 per cent of all Canadian cases of human prion disease. In genetic prion disease, there is a mutation (coding abnormality) in the DNA sequence of the *PRNP* gene, which leads to a difference in the structure of the PrP protein in every cell of the body, and may make conversion of the normal form of PrP into the abnormal form more likely. More than 20 different *PRNP* mutations have now been identified. Genetic prion diseases are subdivided into genetic CJD; Gerstmann-Sträussler-Scheinker disease (GSS); and the very rarely occurring fatal familial insomnia (FFI).



PRNP gene mutations in a person's DNA are responsible for causing hereditary prion disease.

As mentioned above, we all inherit two copies (alleles) of the *PRNP* gene – one from our mother, and one from our father. Genetic CJD, GSS and FFI are all inherited in an autosomal dominant fashion. That is, a person need only possess one abnormal allele of the PRNP gene from their mother or their father to develop disease. A person carrying a mutated allele also has a 50 per cent chance of passing it on to each child. Since CJD does not usually develop until later life, people carrying a mutated *PRNP* allele may pass it to one or more of their children before they become aware that they carry it, or even before they know that the genetic condition is present in their family. In one recent United Kingdom study it was found that the majority of families affected by familial forms of CJD were unaware of the nature of their risk.



Risk of genetic prion disease decreases with more distant genetic relationship to an affected person.

The presence of mutations in the *PRNP* gene can be proven or disproven via a blood test. People with a relative who had CJD and a *PRNP* mutation may therefore choose to find out whether or not they are at risk before any symptoms develop. In most cases where a mutation is found, the person carrying the mutation will develop the disease. Furthermore, it may also be possible to know from the *PRNP* mutation carried, something about what symptoms the disease is likely to cause when it does develop.

Undergoing *PRNP* gene testing is a major decision because at present, as with most genetically caused diseases, there is no way of preventing or curing genetic prion diseases. Testing requires full and informed consent of the patient or their legally eligible representative, and full pre- and post-test support and counselling by a genetic specialist on issues like family planning, insurance and employment. Because results for an individual can have an impact on many family members, if possible these members should also participate in the discussions.

Antenatal testing where a fetus is at risk of carrying a *PRNP* mutation is also possible in principle. The couple might opt for pregnancy termination in a case where a mutation is present, thereby avoiding passing the disease predisposition to a child. This also involves a difficult ethical decision, because a child born carrying a mutated *PRNP* gene is likely to enjoy normal health for many years before the onset of symptoms.

A positive benefit also arises from genetic testing because it is possible to show conclusively if there are no *PRNP* mutations in an affected individual – that is, that their disease was sporadic. In this case, family members carry exactly the same risk of developing CJD as they would if they were unrelated to the affected person – that is, about one chance in a million per year.

What are the symptoms of genetic prion disease?
The symptoms of genetic forms of prion disease vary, depending on the type of *PRNP* mutation involved. There may even be variation in the symptoms among affected members of the same family.

- In genetic CJD the symptoms are similar to that found in sporadic CJD. On average, genetic CJD strikes at an earlier age than the sporadic form: the average age of onset is 55, compared to 65. The course of the disease is often longer, and the patient may survive for several years after the onset of symptoms.

- GSS usually starts with ataxia and progresses to dementia. The disease course is longer on average than it is with CJD, and the patient may survive for several years.

- In FFI the main symptom is a progressive and untreatable form of insomnia. Eventually FFI leads to a breakdown of the brain's control of body functions, coma, and death.

Acquired CJD

Kuru

The first indication that human prion disease might be transmissible came with the discovery among the Fore people of Papua New Guinea in the 1950s of a strange, fatal neurological disease called kuru. Although the disease has almost disappeared, research on kuru has been of great importance in helping us to understand human prion diseases, and in particular, the risks of their being transmitted from person to person.

Iatrogenic CJD

Iatrogenic means "caused by medical treatment". More precisely, this form of CJD is transmitted by contact with infected tissue from someone with the disease.

Because the biochemical processes leading to formation and accumulation of the abnormal, infectious form of PrP can be silently underway for many years before a person becomes ill, there is a period during which accidental transmission to other individuals may occur, from exposure to the affected person's tissues. The prion agent also survives normal disinfection procedures that destroy bacteria and viruses. Thus, some medical procedures involving the brain carry a small risk of accidentally transmitting CJD. For instance, a few people around the world have contracted CJD from brain operations done with instruments that were previously used on a CJD patient. In these cases, the infection was accidentally delivered directly into the brains of the patients who became infected. Nowadays, instruments that are known to have been used on the brain of someone with suspected CJD are destroyed. Transmission of CJD has also occurred with corneal transplants and with grafts of *dura mater*, the tough membrane that covers the brain and was used for many years as a "repair" material in various kinds of neurosurgery. The incubation time for neurologically transmitted iatrogenic CJD is variable, ranging from less than 2 years to over 20 years.

CJD has also been transmitted by treatment with human growth hormone. Before 1985 human growth hormone used to treat children with short stature was prepared from human pituitary glands, its natural source. Typically, 2,000 glands would be pooled to make one batch of growth hormone, which, in turn, would be split into many hundreds of doses and distributed. Therefore, the accidental inclusion of just one gland from someone with unrecognized CJD had the potential to infect many people. To date, there have been no cases of CJD derived from growth hormone diagnosed in Canada. Since 1985, all human growth hormone has been made synthetically, so there is no longer any risk of acquiring CJD from this source.

Lastly, four probable cases of vCJD transmission associated with blood transfusion have been detected in the UK. Of the four infected individuals, three developed clinical vCJD and the fourth succumbed to another illness but was shown to be infected with vCJD.

What are the symptoms of iatrogenic CJD?
Where transmission is directly to the brain, the symptoms are like those of sporadic CJD. However, other forms of iatrogenic CJD are more like kuru, with symptoms of ataxia predominating and dementia being a rare feature.

Variant CJD

"Variant CJD" is so called because it differs in some ways from other forms of CJD (especially in that it occurs in young people).

From 1994 onwards CJD was found increasingly in young people in the UK. By 1996 it was recognized from the age of the patients, symptoms and specific findings under the microscope, that a new type of prion disease had appeared in Britain. This type of CJD was referred to as variant CJD. Since then (until April 2007), 165 of the 202 vCJD cases reported worldwide have occurred in the UK, 22 in France, and the remainder in residents of 9 other countries, including one in Canada that is attributed to the individual's exposure to BSE during a period of UK residence between 1987 and 1990.

Variant CJD has been linked conclusively to exposure of humans to BSE, most likely before the 1989 ban on high-risk bovine tissues (e.g., brain and spinal cord) in the human food supply. However, beyond the demonstration that vCJD and BSE were the same disease, it is still not known precisely how the critical exposures took place and what determines why one individual contracted vCJD while many others, who were exposed to the same food products, did not.

What are the symptoms of vCJD?
The symptoms of vCJD are quite different from those of sporadic CJD. The typical symptoms in vCJD being:

- Relatively young age, with average age at onset of symptoms being 28.
- The first symptoms tend to be psychiatric in nature-anxiety, depression, withdrawal and behavioural changes.
- Persistent pain and odd sensations in the face and limbs.
- After several weeks or months, more clear-cut neurological symptoms may set in, including:
    - Unsteadiness in walking, sudden jerking movements.
    - Progressive dementia.
    - Eventually, the patient loses the ability to move or speak, and will need 24-hour nursing care.
- Death occurs around a year after the onset of symptoms.
- The brains of people with vCJD when examined post mortem show characteristic spongiform change and distinctive (daisy or florid) plaques.

Investigation and diagnosis of CJD

Most physicians are aware of CJD, although because the disease is so rare many have never directly observed a case. A prompt referral to a neurologist should follow reporting of any suspicious pattern of symptoms, where a number of investigations may be carried out, including:

- **Magnetic Resonance Imaging (MRI) of the brain.** This type of scan produces images of the brain. While the MRI is important to rule out other conditions, in a considerable portion of CJD patients there are particular changes to the outer layer (cortex) or inner parts of the brain (basal ganglia and thalamus) that contain nerve cells. These well-defined changes can give a strong indication that CJD is present. The MRI also helps to distinguish sporadic CJD from variant CJD. A computerized tomography (CT) scan of the brain is also frequently used to rule out conditions other than CJD, but it does not show the distinctive changes that are seen with MRI in CJD patients.

- **Electroencephalogram (EEG).** An electroencephalogram, which measures the electrical activity of the brain, may show changes characteristic of classical CJD. However, these changes have not been seen in any cases of vCJD, so EEG is not useful for the vCJD subtype.

- **Brain Biopsy.** Taking a sample of tissue from the brain may be useful in helping reach a diagnosis. If the tissue shows spongiform change, then the diagnosis is often positive. However, the lack of spongiform change does not necessarily mean the person does not have CJD – it could simply mean that the disease has not affected the part of the brain that was sampled. Brain biopsies are not done routinely in CJD. It may be carried out primarily to exclude something other than CJD which may be treatable.

- **Tonsil Biopsy.** Recently, it was shown that PrP^{Sc} can be seen in tonsil tissue in many cases of vCJD, therefore a tonsil biopsy may be useful in diagnosis of vCJD. It is not useful for sporadic CJD.

- **Lumbar Puncture.** In a lumbar puncture, a sample of the cerebrospinal fluid (CSF), which surrounds the brain and spinal cord, is taken by inserting a hollow needle into the lower part of the spinal column, below the spinal cord. Analysis of the CSF may be done for the detection of various “marker” proteins, including one group called “14-3-3 proteins”. Although this test may be used in the context of other clinical data to strengthen the suspicion of CJD, detection of 14-3-3 proteins in the CSF is not in itself sufficiently discriminating to rule in – or rule out – a diagnosis of CJD. Examination of CSF is also done (using other techniques) to exclude infection of the brain (*e.g.*, viral or bacterial encephalitis) as a cause of the symptoms.

- **Blood tests.** Blood and other biochemical tests are usually normal in CJD. A blood sample is used to prepare DNA for genetic sequencing to diagnose inherited forms of prion disease.

- **Autopsy.** Currently, the only way to diagnose CJD with certainty is by examination of the brain after death. The diagnosis usually takes several months. There are five main features which may be found when brain tissue from someone with CJD is examined under a microscope:
    - The brain nearly always shows signs of spongiform change.
    - Increased number of astrocytes - the cells in the brain which support and supply nutrients to neurons - are often seen.
    - Loss of nerve cells is visible.
    - Plaques - deposits of abnormal prion protein - are seen in only 10 per cent of cases of sporadic CJD. However, plaques are seen in some cases of inherited CJD and in all cases of iatrogenic CJD caused by growth hormone treatment. In vCJD, where the brain pathology is very characteristic, a particular type of plaque known as florid plaque is typical of the disease.
    - Accumulated PrP^{Sc} is detectable by means of a technique called immunohistochemistry which uses an antibody that specifically reacts with PrP.

Treatment for CJD

There is no specific treatment or cure, at present, for CJD. What happens on admission to hospital varies. Much depends on the patient, the views of the family and the type of hospital. Following an admission there will be investigation and tests to establish the diagnosis, general supportive nursing care and later on palliative care. There is research underway into the causes of CJD, and into potential treatments.

Canadian Creutzfeldt-Jakob Disease Surveillance System

The Canadian Creutzfeldt-Jakob Disease Surveillance System (CJD-SS) conducts active surveillance for CJD in Canada and is operated by the Public Health Agency of Canada. Drs. Michael Coulthart, Neil Cashman and Gerard Jansen are the joint principal investigators. The CJD-SS aims to collect relevant diagnostic and epidemiologic information about every person with CJD in Canada, obtained through consultation with physicians, antemortem and postmortem laboratory testing, review of medical records, and a detailed family interview. The main purposes are to study the epidemiology and causes of human prion diseases in Canada, and to protect public health by reducing modifiable risks for prion transmission. The surveillance system operates on a reference-services model by offering comprehensive support to referring physicians for laboratory investigations, clinical consultation and education. For more information regarding the Canadian Creutzfeldt-Jakob Disease Surveillance System please contact the clinical co-coordinator, Ms. Elina Olsen RN, at 1-888-489-2999.

Frequently asked questions about CJD

1. ***Can you catch CJD from someone?***
CJD and other human prion diseases are not believed to spread by close or casual person-to-person contact or by the airborne/respiratory route. However, transmission can occur during invasive medical interventions. It is sensible for anyone who might be exposed to the blood of another person to wear gloves.

2. ***How can we be sure that the diagnosis of CJD is the correct one?***
It should be emphasized that a definite diagnosis of any form of CJD can only be given by brain tissue examination after death. Each individual case of CJD can be assigned to one of three subtypes: sporadic, genetic or acquired. The considerations for diagnosis vary depending on the subtype. In genetic prion diseases, the diagnosis depends on development of particular neurological symptoms and the identification of a *PRNP* gene mutation by genetic analysis. Iatrogenic CJD is diagnosed on the basis of a confirmed diagnosis of CJD in someone who had a relevant medical exposure. Variant CJD is diagnosed by distinctive features seen on post-mortem examination of the brain.

3. ***Is the blood supply safe from CJD?***
Since donors cannot, at present, be tested for early biological indicators of CJD, nor can blood donations be tested for the removal of the prion agent after processing, and considering vCJD has been shown to be transmissible through blood transfusion, the Canadian Blood Services has developed policies with regards to CJD and blood donation. Canadian Blood Services deferral policies are available by contacting Canadian Blood Services at 1-888-2donate.

4. ***Is there a risk in contracting CJD from organ transplant surgery?***
The risk of contracting CJD from organ transplants is uncertain, but believed to be small. Unfortunately, a transplant usually has to be done before a full post-mortem examination of the donor can be completed, so this risk cannot be completely eliminated. However, if a potential donor is suspected of having CJD their tissues and organs would not be used for transplantation. Note also that there is a risk of infection in any transplant.

5. ***Is the person with CJD in pain?***
Neurological examination and the EEG of people in the later stages of CJD indicate that they lose awareness of their condition as the disease progresses. In the early stages, however, patients with CJD can develop marked fear, which can be very distressing and is probably associated with visual hallucinations. They may feel discomfort and some of the symptoms of the disease - such as myoclonus, sudden jerking of the limbs - are distressing for caregivers to witness. There are medications which can relieve the symptoms and make the person more comfortable. In vCJD dysesthesia, an unpleasant abnormal sensations to normal stimuli, has been described.

6. ***Is a post-mortem examination necessary in CJD?***
Post-mortem examination is not compulsory when CJD is suspected - the doctor requires the permission of the next of kin. However, because it is the only way, at the moment, to definitively diagnose CJD, this knowledge is often very helpful for families. The autopsy findings and any donated tissues will also be very beneficial to support research into the disease.

7. ***Will there be many more cases of variant CJD?***

As of April 3, 2007, there were 202 cases of vCJD worldwide. If the disease comes from exposure to infected beef products prior to the ban on specified offal in human food in 1989, as is now widely accepted, then there could be more cases if the incubation period is very long. However, without knowing the exact circumstances of infection, or who is most at risk and why, it is currently impossible to predict how many more cases of vCJD there will be.

8. ***What is being done to protect us from CJD?***

At present there is no specific way of protecting people from developing sporadic or familial CJD. Destroying surgical instruments that have been used on certain tissues of people with CJD and not using their organs for transplant guards against iatrogenic CJD. There have also been recent measures taken by the Canadian Blood Services for safeguarding the blood supply from variant CJD.

Acknowledgement:

The Canadian Creutzfeldt-Jakob Disease Surveillance gratefully acknowledges the contribution and participation of Canadian families and physicians.

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